2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ZINC IN THE UNITED STATES

Zinc is ubiquitous in the environment, being released from both natural sources and sources of human origin. Release of zinc into the environment from sources of human origin are from mining, smelting of zinc, lead, and cadmium ores, steel production, coal burning, and burning of wastes. Natural sources of zinc include the weathering of zinc-containing rocks and soils. Ambient background air concentrations of zinc are generally <1 μg/m^3. Zinc is found in soils and surficial materials of the contiguous United States at concentrations between <5 and 2,900 mg/kg, with a mean of 60 mg/kg. The zinc background concentrations in surface waters are usually <50 μg/L, but natural background concentrations in surface waters and groundwater can range from 0.002 to 50 mg/L.

Exposure of the general population to zinc is primarily by ingestion. The average daily intake of zinc from food in humans is 5.2–16.2 mg zinc/day. Zinc is widespread in commonly consumed foods, but tends to be higher in those of animal origin, particularly some sea foods. Meat products contain relatively high concentrations of zinc, whereas fruits and vegetables have relatively low concentrations. Other possible pathways for zinc exposure are water and air. Sources of exposure include drinking water, food, air that is polluted, tobacco products, and occupational exposure. Individuals occupationally exposed to metallic zinc and zinc compounds are those involved in galvanizing, smelting, welding, or brass foundry operations.

2.2 SUMMARY OF HEALTH EFFECTS

The effects of inhalation exposure to zinc and zinc compounds vary somewhat with the chemical form of the zinc compound, but the majority of the effects seen will occur within the respiratory tract. Following inhalation of zinc oxide, and to a lesser extent zinc metal and many other zinc compounds, the most commonly reported effect is the development of "metal fume fever." Metal fume fever is characterized by chest pain, cough, dyspnea, reduced lung volumes, nausea, chills, malaise, and leukocytosis. Symptoms generally appear a few hours after exposure, and are reversible 1–4 days following cessation of exposure. Exposure levels associated with the development of metal fume fever have not been identified, though are generally in the range of 200–500 mg zinc/m^3. Acute experimental exposures to

lower concentrations of zinc oxide (14 mg/m^3 for 8 hours or 45 mg zinc/m^3 for 20 minutes) and occupational exposures to similar concentrations (8–12 mg zinc/m^3 for 1–3 hours and 0.034 mg zinc/m^3 for 6–8 hours) did not produce symptoms of metal fume fever. In contrast, inhalation of zinc chloride generally results in more pronounced damage to the mucous membranes of the respiratory tract, without the effects normally seen in metal fume fever. Symptoms include dyspnea, cough, pleuritic chest pain, bilateral diffuse infiltrations, pneumothorax, and acute pneumonitis, resulting from respiratory tract irritation.

Acute, high-dose oral exposure to zinc compounds generally results in gastrointestinal distress, with symptoms including nausea, vomiting, abdominal cramps, and diarrhea; exposure levels resulting in these effects generally range from 2 to 8 mg zinc/kg/day. Ingestion of zinc chloride may also result in caustic burns of the gastrointestinal tract, particularly the mouth, esophagus, and stomach. Following longer-term exposure to lower doses (~0.5–2 mg zinc/kg/day) of zinc compounds, the observed symptoms generally result from a decreased absorption of copper from the diet, leading to systemic copper deficiency. The most noticeable manifestation of this is anemia, which has been reported in many studies of zinc supplementation in humans. Zinc administration has also resulted in reductions in leukocyte number and function. Available studies have also associated increased exposure to zinc with decreases in high-density lipoprotein (HDL) levels in humans; however, not all studies have confirmed this observation. Long-term consumption of excess zinc may also result in decreased iron status in women, though whether this is a primary or a secondary effect is not presently clear.

In most cases, dermal exposure to zinc or zinc compounds does not result in any noticeable toxic effects. Zinc oxide is used routinely in topical applications including sunscreens and creams designed to assist in wound healing. However, dermal exposure to zinc chloride, and to a lesser extent other zinc salts, can result in severe skin irritancy, characterized by parakeratosis, hyperkeratosis, inflammatory changes in the epidermis and superficial dermis, and acanthosis of the follicular epithelia.

Available studies have not presented evidence of reproductive or developmental effects in humans or animals following inhalation of zinc compounds. Effects on reproductive or developmental end points have been noted in animal studies by the oral route, but generally only at very high (>200 mg/kg/day) exposure levels.

Occupational studies of zinc inhalation have not shown an increase in the incidence of tumors in exposed workers, relative to controls. A single short-term study of zinc chloride inhalation showed an increase in

tumor formation in mice, but not in guinea pigs; however, the study design was insufficient to allow for definitive determination of the potential carcinogenicity of zinc. Available studies of zinc-induced carcinogenic effects in humans and animals have not been sufficient to demonstrate an increase in cancer incidence following long-term oral exposure to zinc compounds.

The primary effects of zinc are on the respiratory and gastrointestinal systems, and on hematological end points. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Respiratory Effects. In general, exposure to zinc and zinc compounds will result in significant effects on the respiratory system only when the exposure is by the inhalation route. A number of cases of acute, high-dose exposure to zinc chloride smoke from military smoke bombs have been reported. In an early study, cough, dyspnea, burning throat, diffuse infiltrates throughout the lung, chemical pneumonitis, and decreased vital capacity were reported. Other studies have also reported respiratory effects of zinc chloride inhalation, including dyspnea, cough, pleuritic chest pain, bilateral diffuse infiltrations, pneumothorax, and acute pneumonitis from respiratory tract irritation. In some studies, more severe effects have occurred, including ulcerative and edematous changes in mucous membranes, fibrosis, subpleural hemorrhage, advanced pulmonary fibrosis, and fatal respiratory distress syndrome.

Acute inhalation exposure to zinc oxide, and to a lesser extent other zinc compounds, may result in the development of "metal fume fever", a condition that results in elevated body temperatures as well as a transient impairment of pulmonary function; the impairment generally ceases a few days after removal from exposure. The impairment of pulmonary function is characterized by reduced lung volumes, a decreased diffusing capacity of carbon monoxide, and an increase in bronchiolar leukocytes. Respiratory symptoms include dryness of the throat and coughing, progressing to substernal chest pain, cough, and dyspnea. In general, the symptoms of metal fume fever resolve within 1–4 days after cessation of exposure and do not lead to long-term respiratory effects. Inhalation of "ultrafine" zinc oxide particles may also result in metal fume fever, as well as histologic damage and inflammation of the lung periphery.

Several animal studies have been conducted to quantify specific effects after acute zinc oxide inhalation. As in human exposure, the respiratory system is the primary site of injury following inhalation exposure.

Gastrointestinal Effects. Nausea was reported by humans exposed to high concentrations of zinc oxide fumes and zinc chloride smoke by inhalation, as well as following oral exposure to zinc chloride and zinc sulfate. Other gastrointestinal symptoms of excess zinc exposure include vomiting, abdominal cramps, and diarrhea, in several cases with blood. In general, exposure levels associated with gastrointestinal effects of zinc have not been reported. It is unclear in the majority of human studies whether the gastrointestinal effects seen following zinc inhalation were due to systemic zinc or were the result of direct contact with the gastrointestinal tract following mucociliary clearance of inhaled zinc particles and subsequent swallowing.

Hematologic Effects. Leukocytosis persisting for approximately 12 hours after fever dissipates is one of the hallmarks of metal fume fever. Such effects have been observed in a number of case reports of occupational and experimental exposure of humans to zinc oxide fumes. Decreased numbers of red blood cells and hemoglobin were found in several workers with 7–20 years of experience in the galvanizing industry. However, there was excess tobacco use and alcohol consumption by workers and possible concurrent exposure to other chemicals (chloride, sulfide), which confound the study results. No anemia was detected among 12 workers exposed for 4–21 years to zinc oxide fumes in the production of brass alloys. These workers may have also been exposed to magnesium, copper, and aluminum.

Treatment-related changes in hematological parameters have been observed in humans and animals after intermediate or chronic oral exposure to zinc or zinc-containing compounds. Zinc-induced hematological changes are the result of competition with copper during absorption from the small intestine, such that a prolonged increase in dietary zinc results in systemic copper deficiency, leading to anemia. Long-term administration (1–8 years) of zinc supplements has caused anemia in humans. A significant reduction in erythrocyte superoxide dismutase activity (47% decrease), hematocrit (4%), and serum ferritin (23%), compared to pretreatment levels, occurred in female subjects who received supplements of zinc gluconate for 10 weeks. Addition of iron supplements resulted in an increase in serum ferritin, but did not reverse the decrease in erythrocyte superoxide dismutase activity. In a similar study, a decrease in erythrocyte superoxide dismutase activity was reported in male volunteers receiving zinc gluconate supplements for 6 weeks.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No inhalation MRLs have been derived for zinc. A number of acute-duration human studies have identified metal fume fever as an end point of concern; however, no study has clearly identified exposure levels that result in metal fume fever. Animal studies corroborate the effects observed in humans; however, the studies are generally limited in the methods utilized, and other possible targets of toxicity were not examined. Only one intermediate-duration inhalation study in humans was located. In this study, exposure levels were not reported; thus, the study could not be used as the basis for the derivation of an intermediate-duration MRL. No exposure-related effects on lung function were observed in a group of welders chronically exposed to zinc; however, the exposure level was not reported. Thus, no chronic-duration inhalation MRL could be derived.

Oral MRLs

No oral acute MRL was derived for zinc. A number of case reports involving acute exposure were located. These reports suggest that the gastrointestinal tract and the pancreas are end points of concern, and that the adrenal cortex and central nervous system may also be affected. However, a great deal of uncertainty exists regarding the exposure levels for these studies. An oral exposure study in sheep was also identified. Because sheep are ruminants, it is doubtful that they are a good model for human toxicity. As no studies sufficient for derivation of an acute oral MRL were available, no value was derived.

- An MRL of 0.3 mg zinc/kg/day has been derived for intermediate oral exposure to zinc.

Two studies in humans, one in men and one in women, have identified effects of oral zinc supplementation on body copper status in subjects given 50 mg supplemental zinc/day. In one, a decrease in erythrocyte superoxide dismutase activity was reported in male volunteers receiving zinc gluconate supplements for 6 weeks (Fischer et al. 1984). In the other, decreases in erythrocyte superoxide dismutase activity, serum ferritin, and hematocrit, were reported in women given daily supplements of zinc gluconate for 10 weeks (Yadrick et al. 1989). Zinc supplementation has been shown to decrease HDL levels with daily doses of at least 50 mg zinc for 12 weeks (Black et al. 1988; Chandra 1984; Hooper et al. 1980). These studies suggest that there is a dose-response trend and that 50 mg/day is the threshold lowest-observed-adverse-effect level (LOAEL) for zinc. Because of its duration, and because it evaluated a more thorough spectrum of end points, the 10-week study in women was chosen as the key study for derivation of an intermediate oral MRL. The MRL was therefore based on hematological

effects, specifically decreases in erythrocyte superoxide dismutase activity, serum ferritin, and hematocrit, in women given daily supplements of 50 mg zinc as zinc gluconate for 10 weeks (Yadrick et al. 1989). The lowest-observed-adverse-effect level (LOAEL) of 0.83 mg/kg/day was calculated from the reported supplemental dose of 50 mg zinc/day, and based on a reference body weight of 60 kg for women. Initially, it was discussed that a correction for background zinc consumption would be included in the MRL calculation. However, when including the background (cited as 9.28 mg/day from the FDA total diet study [Pennington et al. 1996]), the value of the MRL was basically unchanged. Therefore, no background value was included since this adjustment did not occur in the primary study. The MRL was calculated by applying a composite uncertainty factor of 3 (for uncertainties regarding human variability and the use of a minimal LOAEL) to the lowest-observed-adverse-effect level (LOAEL) of 0.83 mg/kg/day.

- The intermediate oral MRL of 0.3 mg zinc/kg/day has been accepted as the chronic oral MRL.

The chronic oral MRL is expected to be without adverse effects when consumed on a daily basis over a long period of time; neither inducing nutritional deficiency in healthy, non-pregnant, adult humans ingesting the average American diet nor resulting in adverse effects from excess consumption. The MRL was not based on a chronic-duration oral study due to a lack of adequate long-term studies in humans and animals. The chronic human study by Hale et al. (1988) provides support for the Yadrick et al. (1989) study and suggests that hematological effects may occur at higher zinc doses. A significant decrease in red blood cells in females receiving daily supplements of up to 2 mg zinc/kg/day for an average of 8 years was reported by Hale et al. (1988). Furthermore, decreases in serum creatinine, total protein, and uric acid and an increase in mean corpuscular hemoglobin (MCH) were observed in the treated male and female subjects (mean age of 78 years) compared to controls. Several other studies have reported copper deficiency-induced anemia resulting from longer-term exposure to zinc, either via supplements or other sources (Broun et al. 1990; Gyorffy and Chan 1992; Hale et al. 1988; Hoffman et al. 1988; Patterson et al. 1985; Porter et al. 1977; Prasad et al. 1978; Ramadurai et al. 1993; Stroud 1991; Summerfield et al. 1992). However, these studies have generally been reports of a single individual, and the level of exposure has not been reliably identified, making them unsuitable for use in deriving a chronic MRL.

In general, the MRL is an estimate of the daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. The MRLs are based on soluble zinc salts; it is less likely that nonsoluble zinc compounds would have these effects at this level.